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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,504	10/19/2001	Steven J. Siegel	P-9565-US	3358

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/046,504	SIEGEL ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 6-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt request for extension of time, request for continued examination under 37 CFR 1.114, declaration under 37 CFR 1.132, amendment and remarks, all filed 03/03/09. No claims i9s currently amended. Claims 1, 3, 4 and 6-10 are pending.

Response to Arguments

Previous rejections that are not reiterated herein have been withdrawn.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/03/09 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The boundaries for the protection sought for "another antipsychotic drug" in claim 10 are

not discernible making the scope of the claims unclear and indefinite.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gander et al. (US 5,648,096) or Dittgen et al. (US 6,303,137).

7. Claim 1 is a composition comprising 20-40% haloperidol and polylactide or lactide-co-glycolide copolymer. The recitation of "surgically implantable drug delivery device" is in the preamble and is the intended use of the composition. Furthermore, fabrication of the device by solvent casting is the method of preparing the composition and implantation of the device under the skin is the intended use of the composition or the route of administration of the composition. Furthermore, delivery of haloperidol from the implant at steady state concentration for 5 months

is the characteristic property derived from the device. Thus claim 1 is appropriately examined as composition claim.

8. Gander: Gander discloses compositions produced according to the scheme in Figure 1, the composition comprises biodegradable polymers such as polylactic acid and poly(lactic-co-glycolic acid) (abstract; column 5, line 52) and an active agent (column 3, lines 9-11). Any active agent can be formulated by the process of Gander as shown by the long list of drugs (see column 6, line 4 to column 7, line 57) indicating that the Gander is not limited to specific drugs. Among the drugs that can be formulated by the process of Gander is haloperidol, a known anti-psychotic drug. Gander also teaches that the composition can be made in the form of microcapsules or implant (column 1, lines 38, 39). Gander does not teach the amount of drug that could be loaded onto the biodegradable polymer. But the artisan would know what amount of drug to incorporate into the biodegradable polymer depending on the amount of drug needed, in the case of the antipsychotic drug, haloperidol, to effect treatment. Therefore, taking the teachings of Gander, one having ordinary skill in the art at the time the invention was made would incorporate drugs such as haloperidol into the biodegradable polymer, polylactic acid or poly(lactic-co-glycolic acid) in amounts that when administered to a subject in need thereof would provide the anticipated treatment. Gander suggests that PLGA having 50:50 lactide:glycolide can be used (column 2, lines 35 and 36) so that claim 4 is met.

9. Dittgen: Dittgen discloses implants (abstract; column 6, lines 4-6) comprising active agents such as verapamil, haloperidol and amitryptiline (column 5, lines 50-58). Dittgen does not say how much drug to use, rather, Dittgen has exemplified the compositions using specific drugs such as testosterone to show %release of the testosterone within 38 days. But the artisan

would know what amount of drug to incorporate into the biodegradable polymer depending on the amount of drug needed, in the case of the antipsychotic drug, haloperidol, to effect treatment. Therefore, taking the teachings of Dittgen, one having ordinary skill in the art at the time the invention was made would incorporate drugs such as haloperidol into the biodegradable polymer, polylactic acid or poly(lactic-co-glycolic acid) in amounts that when administered to a subject in need thereof would provide the anticipated treatment. Poly(lactide-co-glycolde) (PLGA) has percentages of lactides and glycolides and PLGA having 50:50 lactide: glycolide ands other combinations are known in the art such that any PLGA having any combination of the lactide:glycolide can be used. Absent unexpected results, the PLGA having the combination of lactide and glycolide as recited in claim 3 is not inventive over Dittgen.

10. Claims 1, 3, 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gander et al. (US 5,648,096) or Dittgen et al. (US 6,303,137) in view of Nichols (US 5,047,536).

11. Gander and Dittgen have been described above to render obvious claims 1 and 3. Both Gander and Dittgen contemplate the composition in the form of an implant (see paragraphs 6 and 7 above). Gander does not teach method of treating psychosis as required by claims 7-9. Dittgen does not teach method of treating psychosis as required by claims 7-9. But haloperidol is known to treat schizophrenia according to Nichols (column 1, lines 40-42). Since implants are designed for implantation, taking the teachings of Gander or Dittgen in view of Nichols, one having ordinary skill in the art would reasonably expect that implanting the implant of Gander or Dittgen would effectively treat schizophrenia or psychosis. Surgical implantation is one of the ways of implanting drug delivery devices so that claim 8 is met.

12. Claims 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gander et al. (US 5,648,096) in view of Cima et al. (US 5,490,962).

13. Gander describes processes of preparing compositions comprising PLGA and active agents (abstract; column 1, lines 38, 39; column 2, lines 34, 35), the process is shown in the scheme in Fig. 1. For claim 6, Gander suggests that PLGA at 50:50 lactide:glycolide can be used (column 2, lines 34,35) so that the claim 6 is met. Gander teaches spray drying but does not teach the process of solvent casting as required by claim 4. But it is known in the art that solvent casting, solvent extraction, spray drying and compression molding are method use to form tablets, capsules, slabs and microcapsules (see Cima at column 1, lines 32-36). Therefore, taking the teachings of Gander, one having ordinary skill in the art at the time the invention was made would reasonably expect that any of the known methods of solvent casting, solvent extraction, spray drying and compression molding can be used to produce the composition of Gander in the form of implant or microcapsules.

14. Claims 1, 3, 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gander et al. (US 5,648,096) or Dittgen et al. (US 6,303,137) in view of Nichols (US 5,047,536) and further in view of Bymaster et al. (US 6,147,072).

15. Gander or Dittman in view of Nichols has been described above to render obvious claims 1, 3, 7-9. The combined composition does not contain another psycho active agent. But combination therapies using more than one antipsychotic drug have is known in the art to be effective for treating psychosis according to Bymaster (see the title, abstract and column 1, lines 60-65 and column 2, lines 1-9). Therefore taking the teachings of Gander or Dittman in view of Nichols and further in view of Bymaster, one having ordinary skill in the art at the time the

invention was made would reasonably expect that addition of another antipsychotic drug to the haloperidol drug delivery composition would be effective in treating psychosis with greater efficiency.

16. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 for reasons of record and reiterated herein below.

17. Cheng describes haloperidol-loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere (abstract), a 10% haloperidol was achieved (section 3.3 at page 208). "Surgically implantable drug delivery" is in the preamble and represents the intended use of the delivery system while the body of the claim fully defines the claimed composition/product/device. The difference between the claims and Cheng is that the claims recite a range of 20-40% of haloperidol being fabricated into the polymer while Cheng uses 10%. However, it is said on page 209, left column at line 6 that a drug content of from 14.6 to 23.9% can be loaded onto the PLG microspheres. Therefore, taking the teaching of Cheng, one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to formulate haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere in which the drug load is 10% or from 14.6 to 23.9%.

18. Claims 1, 7-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of Domb et al. ("Degradable Polymers

for Site-Specific Drug Delivery," in polymers for Advanced Technologies, Vol. 3, pp. 279-292, 1992 for reasons of record and reiterated herein below.

19. Cheng is discussed above as rendering obvious claims 1 and 3. Cheng acknowledges that haloperidol, an antipsychotic drug, is used to treat psychosis such as schizophrenia by oral dosage forms and also as long acting depot injections (section 1). Cheng administers the haloperidol by injecting the composition as a depot meeting claim meeting the implantation of claim 7 and 9; claim 8 is obvious since drug delivery devices are implanted under the skin. But, implantation/implant reads on depot resulting from depot injections, and it is known to use degradable polymers to deliver drugs to target sites of interest as described by Domb and carries the advantage that implants are used as site specific drug delivery routes. Therefore, taking the teachings of the references together, one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to administer the haloperidol antipsychotic drug by implanting it to a site in the schizophrenic subject that would provide sustained release of the antipsychotic agent for a more effective treatment of the condition.

20. Claims 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of Sidman (US 4,450,150) for reasons of record and reiterated herein below.

21. Cheng prepares the haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere by solvent evaporation (section 2.2). Cheng does not cast the haloperidol dissolved in the solvent in a mold so that Cheng differs from the invention by not molding the

haloperidol-polymer solution. However, it is known that implants that deliver drugs to target sites are molded by compressing or injecting the drug formulation as disclosed by Sidman (column 9, lines 8-12; column 10, lines 51-52; column 18, line 29). Therefore, taking the teachings of the references together, one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to shape the haloperidol antipsychotic drug loaded polymer by injection molding or compression molding to provide a product that would be successfully implanted into the site in the schizophrenic subject that would provide sustained release of the antipsychotic agent for a more effective treatment of the condition.

Response to Arguments

22. Applicant's arguments filed 03/03/09 have been fully considered but they are not persuasive.

23. Applicant's main argument is that Cheng does not teach the concentration of the haloperidol in the polymer and to that extent applicant has presented declarations from Dr. Davis, one of the inventors of the Cheng reference to say that greater than 10% haloperidol cannot be incorporated into the drug delivery device of Cheng. The declaration by Dr. Davis and Dr. Siegel will be addressed in a different section.

24. a) While page 209 of Cheng may be related to 5-fluorouracil, it is noted that the section of page 209 suggests that higher amounts of drugs can be loaded onto the polymer. Furthermore, rejection is not anticipatory of the claimed amounts but a rejection in which the claimed amounts are rendered obvious by the teaching on page 209 that higher amounts of drugs can be loaded.

25. b) The examiner has considered applicant's evidentiary references namely Okada and Lam, to support applicant's contention that higher than 10% haloperidol cannot be loaded onto the PLGA of Cheng but can be loaded onto the PLGA of the invention. However, while Okada and Lam may support applicant's position, the Cheng reference provides a suggestion that higher amounts of haloperidol can be loaded onto the polymer.

26. c) Applicant refers to the Table in Cheng, but, the Cheng reference must be considered as a whole and not just the Examples or Table. It is however disclosed that higher drug concentrations can be loaded on to the polymer. The rejection is not that the composition of Cheng has an amount of 20-40% haloperidol, but that the suggestion points the artisan to optimize the concentration of the haloperidol in the polymer.

27. d) Applicant says that modifying the depot formulation of Cheng would have destroyed the depots and made them inoperable. While this may be so as per applicant's opinion, applicant has not factually shown that modifying the depot formulation of Cheng destroys it. There is no evidence to show that the device of Cheng is inoperable when modified.

28. e) With regards to Domb, it is noted that Domb is not relied upon for 20-40% haloperidol. Rather, Domb is relied upon for teaching that biodegradable polymers are utilized as site specific delivery devices (see second paragraph of the abstract on page 279) using implants (second full paragraph of page 280 at the right column).

29. f) Applicant says that Cheng did not use the method of solvent casting. The examiner agrees and this is why a secondary reference was used to show that implants that deliver drugs to target sites are molded by compressing or injecting.

30. Therefore, Cheng is appropriately applied under 35 USC 103.

31. Declaration under 37 CFR 1.132 by Dr. Davis: The declaration under 37 CFR 1.132 filed 03/03/09 is insufficient to overcome the rejection of claims 1, 3, 4 and 6-10 based upon the rejections under 35 USC 103 over Cheng, and Cheng in view of Domb and Cheng in view of Sidman as set forth in the last Office action because: the declaration is an opinion declaration and does not take the place of factual showing.

32. Declaration under 37 CFR 1.132 by Dr. Siegel: The declaration under 37 CFR 1.132 filed 03/03/09 is insufficient to overcome the rejection of claims 1, 3, 4 and 6-10 based upon the rejections under 35 USC 103 over Cheng, and Cheng in view of Domb and Cheng in view of Sidman as set forth in the last Office action because: the declaration is an opinion declaration and does not take the place of factual showing.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Blessing M. Fubara/
Examiner, Art Unit 1618